

### **REMARKS**

Claims 1-10 and 21-32 were pending in the present application.

Applicants have amended, without prejudice, claims 1, 2, 4, 6-8, 10, 21, 22, 24, 26-28, and 30-32 to clarify that which Applicants regard as the invention. Specifically, claims 1, 21 and 31 have been amended to clarify that the present invention is directed to adenovirus formulations, and methods of preserving the same, with chlorobutanol and a buffer within a pH range of about 6.0 to about 9.0. Support for this amendment can be found in the specification (as published as U.S. Patent Application Publication No. US 2007/0148765 A1), for example, in paragraphs [0031] and [0032]. Claims 2, 4, 6, 8, 10, 22, 24, 26, 28, 30, and 32 have been amended to make it clear that the phrase 0.4% to 0.6% refers to the concentration of chlorobutanol. Claims 7 and 27 have been amended to delete reference to a buffer as language regarding a buffer has been incorporated into the independent claims. Applicants respectfully submit that no new matter has been added by these amendments.

After entry of the amendments, claims 1-10 and 21-32 will remain pending.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

#### ***Claim Rejections – 35 USC § 103***

Claims 1, 2, 9, 10, 21, 22, and 29-32 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gao et al. (WO 01/40455; "Gao"). The Examiner alleges that it would be obvious to one of ordinary skill in the art and well within the ability of the ordinary artisan to determine which concentration of chlorobutanol would have been appropriate for preserving live adenovirus vectors. The Examiner further alleges that it would have been obvious to use a vial to store the contents of the formulation in order to protect the formulation for delivery, storage and subsequent use.

Without admitting to the propriety of a *prima facie* case of obviousness, Applicants have amended the claims to clarify that which Applicants regard as the invention. Specifically, the present invention, as reflected in the amended claims, is directed to adenovirus formulations comprising chlorobutanol and a buffer within a pH range of about 6.0 to about 9.0, and methods of preserving adenovirus formulations by adding chlorobutanol and a buffer within

a pH range of about 6.0 to about 9.0. Applicants respectfully submit that the amended claims are patentable over Gao.

Gao does not teach any buffer having a pH within a range of about 6.0 to about 9.0.

Even assuming *arguendo* that Gao renders the claimed invention obvious (whether alone or in combination with another reference), Applicants rebut any *prima facie* case of obviousness based on obviousness of the pH range. See MPEP § 2144.05.

Applicants respectfully submit that the art teaches away from the claimed invention. First, the art teaches that chlorobutanol is not stable in buffered solutions greater than pH 6. One study demonstrated that buffered chlorobutanol solutions are stable at pH values up to 6, but at higher pH values the chlorobutanol undergoes decomposition. See Taub *et al.*, 1943, J. Amer. Pharm. Assoc. 32:28-31, Table II, p. 30, conclusion 4 and p. 31, col. 1. Another study determined that the optimum pH for stability of buffered solutions of chlorobutanol is 3 to 6. See Patwa *et al.*, 1966, J. Amer. Pharm. Assoc. NS6:372-373. Second, the art teaches that chlorobutanol is not effective as a preservative at a pH of 5 or greater. See Akers, Pharm. Technol. May 1984, pp. 36-46, Table IV. Thus, the art teaches away from using chlorobutanol as a preservative in buffered formulations.

Applicants respectfully submit that the specification also provides unexpected results relative to the prior art. Chlorobutanol present in a formulation buffered at pH 7.4 (A195 buffer) provided effective antimicrobial activity and passed USP criteria and EP criteria B. See the specification, paragraph [0065] and Table 7. Therefore, the claimed formulations provided effective preservative activity where none would be expected based on the teaching of the prior art.

Thus, Applicants respectfully submit that any *prima facie* case of obviousness has been rebutted.

Claims 3-8 and 23-28 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Gao as applied to claims 1 and 21 above, and further in view of Evans et al. (WO 01/66137 A1, "Evans") for reasons of record.

Based on the above, Applicants respectfully submit that the *prima facie* case of obviousness has been rebutted. As Evans fails to remedy the deficiencies of Gao, Applicants respectfully submit that present invention is not obvious over Gao in view of Evans.

Accordingly, for the reasons above, Applicants respectfully submit that rejections under 35 U.S.C. 103(a) have been obviated.

### **CONCLUSION**

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

By /Henry P. Wu, Reg. No. 44,412/  
Henry P. Wu  
Reg. No. 44,412  
Attorney for Applicants

Merck & Co., Inc.  
P.O. Box 2000  
Rahway, NJ 07065-0907  
732.594.5312

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